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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/803,666	03/18/2004	Yuen-Liang Lai	5482-2	6009

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EXAMINER	
PAK, JOHN D	

ART UNIT	PAPER NUMBER
1616	

DATE MAILED: 07/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/803,666	LAI ET AL.	
	Examiner	Art Unit	
	JOHN PAK	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 9/9/05 & 9/22/05
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Claims 1-10 are pending in this application.

It is noted for the record that the Examiner is interpreting the phrase "cutaneous metastatic cancer" to mean cancer that has metastasized to cutaneous sites. Said phrase does not mean cutaneous cancer that has metastasized to other sites.

It is also noted for the record that claim 10 recites a total radiation dose ranging from 30-50 Gy/5 days. In the absence of further clarifying claim language, the Examiner interprets this dose to include 5 non-consecutive days, i.e. a fractionation schedule wherein total of 30-50 Gy is administered on 5 days, but not necessarily on 5 consecutive days.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-10 are rejected under 35 U.S.C. 102(a) as being anticipated by Lai et al.[1]

Lai et al. explicitly disclose treating a human patient having a cutaneous metastatic breast cancer with topical arsenic trioxide in gel form and electron beam radiotherapy (see from the first full paragraph on right column of page 825 to the second

[1] Anti-Cancer Drugs, 2003, Vol. 14, pages 825-828. Accepted for publication on 9/2003, so this article does not qualify as prior art under 35 USC 102(b). But the article does qualify as prior art under 35 USC 102(a) because the list of authors is different that the inventive entity of the instant application.

paragraph on left column of page 826). Arsenic trioxide dose is 0.05 to 0.15 mg/cm^2/day, which is administered 1 hour before daily radiation and removed 5 minutes before irradiation (page 826, left column, second paragraph). Radiation was administered 5 days a week for a total dose of 50 Gy in 25 fractions or 30 Gy in 10 fractions (id.).

The claims are thereby anticipated.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ellison et al. (US 2004/0115283) in view of Cheng[2], the acknowledged prior art and Wu (US 6,127,688).

Ellison et al. disclose arsenic substances such as arsenic trioxide and arsenic sulfides to possess a variety of beneficial anticancer properties, including apoptosis activity, angiogenesis inhibiting activity, differentiating activity, and sensitization of cancer cells to radiation and/or chemotherapy (paragraphs 0031, 0042). Treating

[2] Submitted by applicant in the IDS of 9/9/2005.

primary and metastatic cancers is taught (paragraph 0029), including breast, lung, colon, head and neck cancer in combination with radiotherapy (paragraphs 0030, 0049). More specifically, effective treatments of squamous cell carcinoma, basal cell carcinoma, melanoma, tumors of breast, lung carcinoma and colon carcinoma are disclosed (paragraphs 0051-0053, 0074, 0129). Treatment of metastatic breast cancer and "metastases from breast ... cancer" are disclosed, as well as alleviating or reducing symptoms thereof (paragraph 0103). Any mode of administration of the arsenic substance is disclosed, including topical administration, dermal administration and transdermal patches (paragraphs 0047, 0110). Colloidal suspensions, creams, ointments, pastes are disclosed for arsenic formulation types (paragraph 0048). Arsenic dosage is taught to vary with the severity of the condition to be treated and route of administration, body weight, age, condition and response of the patient (paragraph 0121). Daily dose of 10 μg to 200 mg, including 0.5 mg to about 70 mg of an arsenic active ingredient is disclosed (id).

Cheng et al. establish that breast cancer commonly affects the skin and cutaneous metastases frequently recur in chest wall or scalp (first English sentence). Cheng et al. disclose a topical formulation of arsenic trioxide for treatment of skin lesions metastasized from the breast (first English paragraph). Clinical evidence of improved dryness of skin lesions and reduced unpleasant odor is reported (first English

paragraph, near the end on second English page). Systemic absorption of topically applied arsenic lotion could not be observed (id.).

Applicant acknowledges the following in the instant specification:

(1) Arsenic trioxide is known to inhibit growth of many cancer cell lines and promote apoptosis in the cancer lines (page 3, lines 11-13);

(2) Arsenic trioxide is known to sensitize human cervical cancer cells to ionizing radiation in vivo and arsenic trioxide pre-treatment + ionizing radiation is known to have a synergistic effect with respect to decreased clonogenic survival and regression of established human cervical tumor xenografts (page 3, lines 10-14);

(3) Cheng et al., supra, disclose topical arsenic trioxide to improve local tumor control and decrease wound secretion without significant systemic or local effects (page 3, lines 17-19).

Wu is cited solely to establish that "principal applications" of electron beam radiotherapy are for treatment of skin cancer, head and neck cancer, and chest well irradiation for breast cancer (column 1, lines 24).

Ellison et al. do not expressly disclose treating a human patient having a cutaneous metastatic cancer, e.g. cutaneous metastatic breast cancer, by topically administering to the site of said cutaneous metastatic cancer an arsenic substance such as arsenic trioxide and transcutaneously applying an electron beam to the site, with optional step of removing the arsenic substance before applying the electron beam.

Ellison et al. also do not expressly disclose a gel arsenic formulation and daily arsenic dose in terms of mg/cm^2. However, for the reasons set forth below, such differences and the claimed invention as a whole would nonetheless have been obvious to the ordinary skilled person in this art.

While Ellison et al. do not expressly disclose treating a human patient having a cutaneous metastatic cancer, e.g. cutaneous metastatic breast cancer, by topically administering to the site of said cutaneous metastatic cancer an arsenic substance such as arsenic trioxide, Ellison et al. teach treating metastatic breast cancer, effective treatments of squamous cell carcinoma, basal cell carcinoma, melanoma, tumors of breast, lung carcinoma and colon carcinoma are disclosed (paragraphs 0051-0053, 0074, 0129). Ellison et al. teach treating metastatic breast cancer and "metastases from breast ... cancer," as well as alleviating or reducing symptoms thereof (paragraph 0103). Further, Ellison et al. teach that arsenic trioxide provide the advantage of sensitization of cancer cells to radiation and/or chemotherapy (paragraphs 0031, 0042). Topical and dermal administration and myriad topical formulations such as colloidal suspensions, creams, ointments and pastes are further taught by Ellison et al. Hence, the ordinary skilled artisan in this field would have been sufficiently motivated to topically administer arsenic trioxide to cutaneous metastatic breast cancer in combination with radiation therapy in combination with radiation therapy. Gel

formulation would have been obvious from the various topical and dermal formulations taught by Ellison et al., including colloidal suspensions, creams, ointments and pastes.

As for the specific use of electron beams, it is noted that principal applications of electron beam radiotherapy are for treatment of skin cancer, head and neck cancer, and chest well irradiation for breast cancer. Therefore, the ordinary skilled artisan would have been motivated to select such radiation therapy for treating cutaneous metastatic breast cancer.

Applicant's claims 8-9 recite arsenic daily dose in mg/cm^2. Simple conversion with the standard average of 1.8 m^2 (18,000 cm^2) for an average 70 kg adult shows that applicant's claimed daily dose range approximates to about 180 mg to 9,000 mg (claim 8) and 900 mg to 2,700 mg (claim 9). Applicant's claim 8 is met by Ellison's daily dose of up to 200 mg. As for applicant's claim 9, Ellison et al. teach that arsenic dosage is to vary with the severity of the condition to be treated and route of administration, body weight, age, condition and response of the patient (paragraph 0121). Therefore, in view of the fact that topically applied arsenic lotion is not systemically absorbed (Cheng et al.), one of ordinary skill in the art would have been motivated to increase the arsenic concentration/dose in the topical or dermal application to treat cutaneous site of cancer. Keeping arsenic low when administered non-topically is important for balancing the anticancer effect of arsenic with the toxicity of arsenic; but given the lack of systemic absorption in topical administration, one having ordinary skill in the art would have been

motivated to increase the dose for increased potency. Consequently, applicant's daily dose range as recited in claim 9 would have been fairly suggested by the combined teachings of the prior art.

Lastly, with respect to claim 2, wherein removal of the arsenic pharmaceutical composition from the cutaneous cancer site is required, it is the Examiner's position that such a step would have been a routine step in the transcutaneous application of electron beams, wherein clear and unhindered access to the site is advantageous.

Therefore, the claimed invention, as a whole, would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, because every element of the invention and the claimed invention as a whole have been fairly disclosed or suggested by the teachings of the cited references.

Claims 1-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ellison et al. (US 2004/0115283) in view of Cheng, the acknowledged prior art, Medline abstract 95357499, Medline abstract 84139233, and Wu (US 6,127,688).

Teachings of Ellison et al., Cheng et al., the acknowledged prior art, and Wu have been discussed in the preceding ground of rejection, and the discussion there is incorporated herein by reference.

The two Medline abstracts are cited to establish the obviousness of the total radiation dose of 30-50 Gy/5 days (claim 10).

Medline abstract 95357499 discloses accelerated radiotherapy to have the potential to increase local control of rapidly growing tumors. 2 Gy per fraction, 8 hours between fractions, for a total of 50 Gy is disclosed for treatment of breast cancer patients. This calculates to 6 Gy per day and 30 Gy/5 days.

Medline abstract 84139233 discloses large dose of irradiation to provide beneficial anticancer results. Disclosed is 10 Gy at 3 times a week for a total of 30 Gy by betatron electron in advanced breast cancer. This equals 30 Gy/3 days.

Complete rationale for obviousness of claims 1-9 has been set forth in the preceding ground of rejection, and the discussion there is incorporated herein to avoid repetition. Claim 10 differs from the cited references in that no one single reference specifically discloses arsenic + electron beam transcutaneously applied in a total radiation dose of 30-50 Gy/5 days to treat a human patient having a cutaneous metastatic cancer. However, except for the specific total radiation dose, the rest of the invention feature has already been discussed as being obvious for the reasons stated above. With respect to a total radiation dose of 30-50 Gy/5 days, the two Medline abstracts establish that accelerated radiotherapy for breast cancer treatment, total dose up to 50 Gy, and 30 Gy/5 days are all known treatment techniques to aggressively treat breast cancer, advanced cancer in particular. One having ordinary skill in this art is a highly skilled and educated physician with at least an MD and/or PhD, with a specialty in oncology and/or radiation oncology. To such an ordinary skilled artisan in this field,

30-50 Gy/5 days would have been an obvious and routine optimization of fractionation schedule to aggressively treat metastatic cancer that has invaded cutaneous sites, particularly when there are few other viable treatment options left. Motivation to optimize arises from the known benefit of accelerated radiotherapy and larger doses of radiation to treat advanced cancers.

Therefore, the claimed invention, as a whole, would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, because every element of the invention and the claimed invention as a whole have been fairly disclosed or suggested by the teachings of the cited references.

For these reasons, all claims must be rejected at this time.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to JOHN PAK whose telephone number is **(571)272-0620.** The Examiner can normally be reached on Monday to Friday from 8 AM to 4:30 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's SPE, Johann Richter, can be reached on **(571)272-0646**.

The fax phone number for the organization where this application or proceeding is assigned is **(571)273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JOHN PAK
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